Flavonoids (kaempferol, naringin, quer cetin) and furanocoumarins (bergamottin) contained mostly in different kinds of grapefruits may inhibit the function of cytochrome P450 partially or completely, affecting concentration of drugs in the blood. This interaction is not meaningless for the routine everyday practice, therefore an interval between the consumption of the grapefruit or its juice, and taking drugs should be recommended.

Is Eating Seville Oranges Dangerous?

Karolina Kloda1, Karina Sznabel1, Ewa Marcjan2, Artur Mierzecki1#

1. Independent Laboratory of Family Physician Education, Pomeranian Medical University in Szczecin, Poland
2. Clinical Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University in Szczecin, Poland

#Corresponding author: Artur Mierzecki Assoc. Prof., Independent Laboratory of Family Physician Education, Pomeranian Medical University in Szczecin, Rybacka 1, 70-204 Szczecin, Tel/fax: +48 91 48 00 871, e-mail: wikarla@gazeta.pl

RUNNING TITLE Exotic fruits and P450
KEYWORDS cytochrome P450, drugs metabolism, exotic fruits, immunosuppression, xenobiotics
WORD COUNT 1 212
CONFlict OF INTERESTS no conflicts of interest

ABSTRACT

Background. Grapefruits are commonly recognized as a cause of drugs interactions through affecting the cytochrome P450 (CYPs). Large and diverse family of CYPs are protein enzymes with monoxygenase activity involved in both, the activation and detoxification metabolism of xenobiotics. Because of their function, they have been widely researched in vitro and in vivo. There are reports that different exotic fruits have effect on CYP proteins. The aim of this paper is to review recent research articles in order to identify fruits and their juices interfering with the metabolism of drugs and thus endangering the treatment of chronic diseases.

Material and Methods. A systematic review of the literature from PubMed resource with access to MEDLINE was performed. Summaries were obtained from 15 articles published between 1997 and 2014 and closely related to the given keywords. Of these 15 articles, 4 (published between 2002-2012) were fulfilling the pre-determined criteria and were assessed in details.

Results and conclusion. Seville oranges and their juice can endanger the treatment of chronic diseases through inhibition of cytochrome P450 and drug interactions. The diet of transplanted organ recipients should be controlled and they should avoid not only grapefruit, but also Seville orange consumption.
INTRODUCTION

The cytochrome P450, an interesting family of protein enzymes (CYPs), is involved in both, the activation and detoxification metabolism of xenobiotics. Moreover, CYPs catalyze several important for body function reactions: cholesterol and steroid hormones synthesis, bile salts and metabolism of antibiotics, benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, antihypertensive and lipid-lowering drugs [1]. It is estimated that almost three quarters of preparations are subject to transformation by CYPs and from these almost 90% of metabolism can be accounted for 5 human P450s [2]. Genetic studies in humans indentified nearly 20 groups of the cytochrome P450 isoenzymes encoded by different genes [3,4]. CYPs have been widely researched in experiments carried out on microsomes and hepatocytes isolated from the human liver. In vivo studies are based on animal (mice, rats) and humans models [5].

Flavonoids (kaempferol, naringin, quercetin) and furanocoumarins (bergamottin) contained mostly in different kinds of grapefruits may inhibit the function of cytochrome P450 partially or completely, affecting concentration of drugs in the blood [6]. This interaction is not meaningless for the routine every day practice, therefore an interval between the consumption of the grapefruit or its juice, and taking drugs should be recommended. Also other fruits, especially citruses, containing flavonoids and furanocoumarins may influence the cytochrome P450 function [7]. However, there are few studies done on substances interfering with CYPs function, present in rarely eaten citruses, exotic fruits and their juices. Apart from the tropical zone, climate of some regions, especially European and North-American, it is not conducive to the cultivation of citrus and exotic plants, but their fruits and juices are imported from abroad and are becoming more widely available for purchase. Although some of these fruits may be considered luxury and unusual, the number of people consuming them is increasing. Moreover, pulps and juices from citruses and exotic fruits are used in common beverages and preparations. What’s most important, the access to purchasing them is no longer seasonal, but unlimited and obviously not controlled. Therefore, the influence of diet on the treatment process is sometimes overlooked in daily practice because of its time-consuming nature and huge workload. All these problems were already mentioned by authors elsewhere [8].

The aim of this paper is to review recent research articles in order to identify fruits and their juices affecting the P450 cytochrome and thus, interfering with the metabolism of commonly used drugs endangering the treatment process.

MATERIAL AND METHODS

A systematic review of the literature from PubMed resource with access to MEDLINE was performed. Specific combination of key words was entered into the search engine on September 9th 2014: P450 cytochrome; CYP; Seville orange; juice; citrus; drug metabolism; healthy volunteers. Summaries were obtained from 15 articles published between 1997 and 2014 and closely related to the given keywords. Next, all papers found, were checked by the two independent reviewers against pre-determined criteria for eligibility and relevance (original research article; citrus and/or exotic fruits and their juices interactions with commonly used drugs; in vivo human studies with samples >10 adult patients; possible clinical implications of the study in everyday practice). Of these 15 articles, 4 (published between 2002-2012) were fulfilling the pre-determined criteria and were assessed in details. In case of disagreement between the reviewers, the problems were solved through discussion and consensus. Statistically significant results were considered for p < 0.05.

RESULTS

The detailed results of systemic review are presented in Table 1.

DISCUSSION

The effects of grapefruit juice on drugs metabolism have been well established. However, studies on other citrus fruits and exotic fruits are rare. A study by Penzak et al. evaluated the influence of grapefruit juice and Seville orange juice on CYP3A4 modulation and indinavir pharmacokinetics in 13 healthy volunteers. The authors aimed at assessment of intestinal fraction of CYP3A4. They found that coadministration of Seville orange juice and indinavir resulted in a statistically significant increase in indinavir t(max) (1.87 [1.65-2.22] vs. 1.25 [1.03-1.60] h; p<0.05) without altering other pharmacokinetic parameter values. However, this effect did not alter the systemic availability of indinavir. Therefore, the influence of Seville orange juice appeared to be small [9]. These observations are relevant, because Seville orange, also called sour orange, is a pomelo and mandarin hybrid and is widely used in the food industry. Especially in the production of marmalade and flavoring essential oils. Thus, the possibility of dietary intake of Seville orange and its juice is high.

Schwarz et al. described an important problem of affecting the treatment results through, usually not controlled, diet [10]. Recipients of transplanted organs should take immunosuppressants in order to maintain the organ function and minimise the risk of rejection. Even slight differences in blood levels of these drugs, may cause toxic damage to the transplanted organ or not suppress the immune system sufficiently. Therefore, an analysis of beverages containing citrus juice on the concentration of
immunosuppressive drug - cyclosporine in humans has been performed. The study was based on the reports that in patients after lung transplantation who were consuming citrus beverage, the concentrations of cyclosporine in blood level increased twice. Furanoocoumarins inhibiting cytochrome P450, contained in fruit juices turned out to be endangering the treatment process. The authors examined 12 healthy Caucasian volunteers, who were given cyclosporine and two citrus beverages (carbonated Sun Drop and Fresca), and a grapefruit juice without additives, which increased the cyclosporine blood concentration of 180%. Surprisingly, citrus drinks were not changing the drug levels significantly. However, only two beverages were administrated in this study and the market is full of citrus drinks. Therefore, the researchers conclude that diet of organ recipients should be controlled and beverages containing a mixture of juices from citrus fruits should be administered with caution. Moreover, they see the need for further research in this area in graft recipients, because not controlled diet can have serious implications for the outcome of organ transplantation[10].

Guo et al. tested the inhibition of CYPs by furanoocoumarins and response to felodipine in vitro and in vivo. Fruit juices of 3 different pomelos were selected and administered to 12 healthy males with felodipine tablet. It was found that all studied juices inhibited CYP3A in vitro with different potency. Moreover, after administration of pomelo juice higher heart rates in humans were observed. Therefore, authors stated that furanocoumarins caused pomelo juice-drug interaction[11]. This is an important conclusion, relevant for the everyday practice, showing that diet can significantly affect the treatment process. Wason et al. assessed the influence of grapefruit and Seville orange juices on the pharmacokinetic properties of colchicine in healthy volunteers. Administration of grapefruit juice did not significantly affect the parameters of colchicine, whereas Seville orange juice did affect the C(max) and AUC, which were decreased by −24% and −20%, respectively. Although the Seville orange juice reduced the absorption of colchicines, the clinical significance of this finding is unknown. Therefore further studies are needed to explore the treatment process endangering the potential of Seville orange juice, especially that it is more widely present on the market and in form of preparations like beverages, jelly, marmalade and consumable additives[12].

CONCLUSIONS

Seville oranges and their juice can endanger the treatment of chronic diseases through inhibition of P450 cytochrome and drug interactions. The diet of transplanted organ recipients should be controlled and not only should they avoid grapefruit, but also Seville orange consumption.

CITE THIS AS

MEDtube Science 2015, Jun 3(2), 16 - 18

TAB. 1. OVERVIEW OF THE MAIN LITERATURE FINDINGS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sample: Volunteers</th>
<th>CYP</th>
<th>Fruits/juices</th>
<th>Drugs interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penzak et al.</td>
<td>2002</td>
<td>13 healthy</td>
<td>3A4</td>
<td>Seville orange juice, grapefruit juice</td>
<td>indinavir</td>
</tr>
<tr>
<td>Schwarz et al.</td>
<td>2006</td>
<td>12 healthy</td>
<td>3A4</td>
<td>citrus sodas, grapefruit juice</td>
<td>ciclosporin</td>
</tr>
<tr>
<td>Guo et al.</td>
<td>2007</td>
<td>12 healthy</td>
<td>3A</td>
<td>fruit juices of three pomelos (Citrus paradisi, Guanximijou and Changshan-huyou)</td>
<td>felodipine</td>
</tr>
<tr>
<td>Wason et al.</td>
<td>2012</td>
<td>44 healthy</td>
<td>3A4</td>
<td>Seville orange juice, grapefruit juice</td>
<td>colchicine</td>
</tr>
</tbody>
</table>

BIBLIOGRAPHY